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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/706,701 | 11/12/2003 | Paul Lehmann | 21435 | 5722 |

151 7590 09/01/2005

HOFFMANN-LA ROCHE INC.
PATENT LAW DEPARTMENT
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| EXAMINER | |
|---|---|
| ROBINSON, HOPE A | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1656 | |

DATE MAILED: 09/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/706,701 | LEHMANN ET AL. | |
| | Examiner | Art Unit | |
| | Hope A. Robinson | 1656 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *14 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 November 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/29/04;3/10/04;2/13/04*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Application Status*

1. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1656

2. Claims 1-14 are pending and are under examination.

### *Specification*

3. The specification is objected to because of the following informalities:

The specification is objected to because on page 1, the priority information is not provided, for example, "This application claims foreign priority to EP 02026342.2, filed November 22, 2002".

### *Drawing*

4. The drawings are objected to because Figure 1 has a sequence, however, no sequence identifier is present. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be

removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance. Applicant is reminded to file Formal Drawings.

***Information Disclosure Statement***

5. The Information Disclosure Statement filed on April 29, 2004, March 10, 2004 and February 13, 2004 has been received and entered. The references cited on the PTO-1449 Form have been considered by the examiner and a copy is attached to the instant Office action.

***Claim Objection***

6. Claim 8 is objected to because of the following informalities:

Claim 8 is objected to because the claim is missing the article "a" on line 10, where the claim recites "wherein R is lower-alkyl" which should be " wherein R is a lower-alkyl".

Correction is required.

***Claim Rejections - 35 USC ∋ 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 8-14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is directed to a method of treating disturbances in iron distribution by administering human erythropoietin, wherein the erythropoietin protein is a conjugate, said conjugate comprising an erythropoietin protein having at least one free amino group and having the *in vivo* biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells and selected from the group consisting of human erythropoietin and analogs thereof ...", thus the claims encompass fragments. The specification does not demonstrate retention of function for the fragments to demonstrate possession of the genus as claimed in the invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. See *Lockwood*

*v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir.1997)*. Additionally, the specification fails to provide any additional representative species of the claimed genus to show that applicant was in possession of the claimed genus. A representative number of species means that the species, which are adequately described, are representative of the entire genus. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, disclosure of drawings, or by disclosure of relevant identifying characteristics, for example, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

Therefore, for all these reasons the specification lacks adequate written description, and one of skill in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

8. Claims 3-14 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter, which applicant (s) regard as their invention.

Claims 3-14 lack clear antecedent basis for "the erythropoietin protein" claim 1 recites "human erythropoietin".

Claims 8 and 11 lacks clear antecedent basis as the claims recite "the erythropoietin protein is a conjugate" and independent claim 1 recites, "human erythropoietin", thus there is no recitation of "protein" or "conjugate". Claims 8 and 11 also lack clear antecedent basis for the recitation of "an erythropoietin protein" because this language reads on more than one protein and fragments, which has no basis in claim 1.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Silverberg et al. (Journal of the American College of Cardiology, vol. 37, no. 7, pages 1775-1780, February 2001).

Silverberg et al. disclose a treatment method for anemia (disturbance of iron) in patients with congestive heart failure (claim 2) by administering erythropoietin (EPO)

and intravenous iron (claim 1, see page 1775 of the reference). Although the reference does not explicitly teach epoetin alfa or beta, the claim is anticipated as an inherent property of erythropoietin and claim 3 recites the two types in the alternative. Therefore, the limitations of the claims are met by this reference.

***Claim Rejections - 35 USC ∋ 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103 (a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103 (c) and potential 35 U.S.C. 102 (f) or (g) prior art under 35 U.S.C. 103 (a).

11. Claims 1-14 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Silverberg et al. (Journal of the American College of Cardiology, vol. 37, no. 7, pages 1775-1780, February 2001) in view AMGEN INC. (EP640 619, March 1, 1995) and HOFFMANN-LA ROCHE (EP 1064 951, January 3, 2001 (cited on IDS - February 13, 2004).

Silverberg et al. disclose a treatment method for anemia (disturbance of iron) in patients with congestive heart failure (claim 2) by administering erythropoietin (EPO) and intravenous iron (claim 1, see page 1775 of the reference). As Silverberg et al. teach erythropoietin, the recitation of epoetin alfa or beta in claim 3 is obvious, as it could be one or the other. Further, darbepoetin is known in the art for treating anemia (claim 6). Silverberg et al. does not expressly teach a modification of 1 to 6 glycosylation sites (claim 5) or pegylated erythropoietin, (claim 7) however, AMGEN INC. teach erythropoietin having at least one additional site for glycosylation or a rearrangement of at least one site for glycosylation and analogs of the claimed protein (claim 8, see abstract of AMGEN INC.). However, AMGEN INC. does not teach a pegylated erythropoietin. In-so-far-as Silverberg et al. and AMGEN INC. do not teach a pegylated erythropoietin, HOFFMANN-LA ROCHE teach conjugates with erythropoietin with PEG as recited in claims 7-14 (see pages 1-5 of the reference). Additionally, HOFFMANN-LA ROCHE teach the structure recited in claim 4 and glycosylation (claim 5).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to have a method of treating disturbances in iron

in a patient suffering from heart disease comprising administering human erythropoietin because Silverberg et al. teach administration of erythropoietin and iron to treat anemia (iron disturbance) in patients suffering from heart disease. In addition, AMGEN INC. teach analogs of erythropoietin and the introduction of 1 to 6 glycosylation sites and HOFFMANN-LA ROCHE teach a pegylated erythropoietin, conjugates and the chemical structures claimed. One of ordinary skill in the art would be motivated to combine the teachings of the references because erythoropoietin is known in the art to treat anemia (iron disturbance) in patients with heart conditions. In addition, one of ordinary skill in the art would be motivated to increase the glycosylation sites in the protein because AMGEN INC. disclose that erythropoietin has three N-linked and one O-linked site, and that erythropoietin possesses *in vivo* biological activity only when it is sialylated to avoid its binding by the hepatic binding protein" (see page 2 of AMGEN INC), hence more gylcosylation is a benefit. Further, HOFFMANN-LA ROCHE teach erythropoietin for the same purpose and that as a conjugate to PEG an increased half-life is achieved. In addition, HOFFMANN-LA ROCHE teach glycosylation of erythropoietin. Thus, the claimed invention was obvious to make and use at the time it was made and was *prima facie* obvious.

12. Claims 1-14 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Silverberg et al. (Journal of the American College of Cardiology, vol. 37, no. 7, pages 1775-1780, 2001) in view HOFFMANN-LA ROCHE (EP 1064 951, January 3, 2001 (cited on IDS - February 13, 2004).

Silverberg et al. disclose a treatment method for anemia (disturbance of iron) in patients with congestive heart failure (claim 2) by administering erythropoietin (EPO) and intravenous iron (claim 1, see page 1775 of the reference). As Silverberg et al. teach erythropoietin, the two alternative types listed in claim 3 is obvious, as it could be one or the other. Further, darbepoetin is known in the art for treating anemia (claim 6). Silverberg et al. does not expressly teach the addition of 1 to 6 glycosylation sites (5) or pegylated erythropoietin (claim 7) however, HOFFMANN-LA ROCHE teach glycosylation of erythropoietin (see page 2 of the reference); and pegylated erythropoietin conjugates and the chemical structures claimed (see claim 4 and 7-14, pages 1-5 of the reference).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to have a method of treating disturbances in iron in a patient suffering from heart disease comprising administering human erythropoietin because Silverberg et al. teach administration of erythropoietin and iron to treat anemia in patients suffering from heart disease and HOFFMANN-LA ROCHE teach erythropoietin that is glycosylated, pegylated and conjugated. One of ordinary skill in the art would be motivated to combine the teachings of the references because erythoropoietin is known in the art to treat anemia (iron disturbance) in patients with heart conditions and HOFFMANN-LA ROCHE teach that as a conjugate to PEG increases the half-life of the protein in circulation. Thus, the claimed invention was obvious to make and use at the time it was made and was *prima facie* obvious.

***Basis For NonStatutory Double Patenting***

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. Claims 1 and 3-14 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 3-12 of copending Application No. 10/634,477. An obvious-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim

is either anticipated by, or would have been obvious over, the reference claim(s). *See In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); and In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).* Although the conflicting claims are not identical, they are not patentably distinct from each other.

The instant application claim 1 is directed to a method of treating disturbances in iron distribution in a patient suffering from heart disease comprising administering a therapeutically effective amount of human erythropoietin. The dependent claims hereto are directed to an erythropoietin that is epoetin alfa or beta (claim 3); SEQ ID NO:1 (claim 4); a modification of 1 to 6 glycosylation sites (claim5); a darbepoetin (claim 6); pegylated (claim 7); and a conjugate having a particular structure as set forth in claims 8-14. The copending application claim 1 is directed to a method of treating disturbances in iron distribution in a patient suffering from diabetes comprising administering a therapeutically effective amount of human erythropoietin. The dependent claims hereto are directed to an erythropoietin that is epoetin alfa or beta (claim 3); SEQ ID NO:1 (claim 4); a modification of 1 to 6 glycosylation sites (claim5); a darbepoetin (claim 6); pegylated (claim 7); and a conjugate having a particular structure as set forth in claims 8-12. The instant application claims differ from the copending application in that the patient is suffering from heart disease, whereas the copending application patient is suffering from diabetes, however, the methods have one step, administering erythropoietin, thus the resulting effect will be the same. Moreover, the art generally recognizes that heart disease is a risk with diabetes, for example type II

diabetes. Thus, the two sets of claims differ in scope but are obvious one over the other, as the intended use does not materially change the composition administered.

15. Claims 1 and 3-14 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 4-12 of copending Application No. 11/013,560. An obvious-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). *See In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); and In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).* Although the conflicting claims are not identical, they are not patentably distinct from each other.

The instant application claim 1 is directed to a method of treating disturbances in iron distribution in a patient suffering from heart disease comprising administering a therapeutically effective amount of human erythropoietin. The dependent claims hereto are directed to an erythropoietin that is epoetin alfa or beta (claim 3); SEQ ID NO:1 (claim 4); a modification of 1 to 6 glycosylation sites (claim 5); a darbepoetin (claim 6); pegylated (claim 7); and a conjugate having a particular structure as set forth in claims 8-14. The copending application claim 1 is directed to a method of treating disturbances in iron distribution in a patient suffering from chronic inflammatory intestinal disease comprising administering a therapeutically effective amount of human

erythropoietin. The dependent claims hereto are directed to an erythropoietin that is epoetin alfa or beta (claim 4); SEQ ID NO:1 (claim 5); a modification of 1 to 6 glycosylation sites (claim 6); a darbepoetin (claim 7); pegylated (claim 8); and a conjugate having a particular structure as set forth in claims 9-15. The instant application claims differ from the copending application in that the patient is suffering from heart disease, whereas the copending application patient is suffering from chronic inflammatory intestinal disease, however, the methods have one step, administering erythropoietin, thus the resulting effect will be the same. Thus, the two sets of claims differ in scope but are obvious one over the other, as the intended use does not materially change the composition administered.

***Conclusion***

16. No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hope A. Robinson whose telephone number is 571-272-0957. The examiner can normally be reached on Monday-Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr, can be reached at (571) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Hope Robinson, MS

Patent Examiner

8/29/05

HOPE ROBINSON
PATENT EXAMINER